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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-13,15-28 and 125-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-13,15-28 and 125-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 17, 2002 has been entered. The species as claimed in claims 11 and 13 have been rejoined for examination.

Claims 1, 3-5, 8, 11-13, 125, 127, and 130 have been amended, claims 2, 10, and 14 have been canceled, and claims 131-132 have been added by the amendment August 17, 2002.

Claims 1, 3-9, 11-13, 15-28, and 125-132 are pending.

The rejection under 35 USC 112, first paragraph has been withdrawn by the examiner. All of currently pending claims are directed to just a method of inducing a mucosal immune response *in vivo*, and as such, and further in view of the state of the prior art of record, the Davis Declaration, and applicant's response on pages 9 and 10, a reasonable person skill in the art would have no undue experimentation to make and use a CpG oligo as claimed for the purpose of just simply to enhance an induction of a mucosal immune response in a subject including those subjects undergoing a therapeutic or prophylactic treatment with an anti-infectious agent.

However, the currently pending claims are not free of the prior art, as evidenced by the totality of the prior art as set forth during the prosecution of this as-filed application. In view of applicant's amendment to the claims, the followings are new grounds of rejection.

Claims 131 and 132 are rejected under 35 USC 102(e) as being anticipated by Hutcherson (US Pat No. 6,727,230 B1) or Agrawal (US Pat No. 6,526,334).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by an administration to the mucosal surface of subject in need of an mucosal immune response *e.g.,* inhalation or ntranasal administration to a subject exposed to an antigen such as tumor antigen, viral particles, dust, pollen, antigenic molecules contained in the air or in contact with the subject, of an oligonucleotide (which can be complexed with any known colloidal dispersion system including lipid based system) having a length of 8 to 100 nucleotide residues and comprising CpG motif containing oligonucleotide having the generic formula: 5' X1X2CGX3X4 3' wherein C is unmethulated, and wherein X1, X2, X3 and X4 is any nucleotide residue.

Hutcherson teaches a method of stimulating a local immune response in selected cells or tissues of an infectious subject or tumor bearing subject, the method comprising inhaling or administering intranasally (see column 7, column 1, last first par.) to the subject a synthetic or ISIS oligo containing an unmethylated CpG motif, see the sequence listing as set forth in columns 15 and 16. Ophthalmical, vaginal or rectal administration is also

disclosed depending on a target tissue or cells targeted for an administration. While Hutcherson does not teach explicitly that functional property of a mucosal immune response has been generated as the result of an administration of an ISIS oligo to the mucosal surface, such must necessarily follow as the result of the administration, particularly since both methods disclosed in Hutcherson and the claims are identical. Note that a human subject who is identified as a cancer patient or one having an infectious agent is the same subject that is exposed to an antigen not encoded in a nucleic acid vector.

Agrawal teaches a method of stimulating an immune response and/or cytokines production in an infectious animal or tumor bearing animals, the method comprising administering intranasally (see column 5, lines 40-56) to the subject a synthetic oligo containing an unmethylated CpG motif, wherein the oligo has the generic formula: 5' X1X2CGX3X4 3' wherein C is unmethulated, and wherein X1, X2, X3 and X4, see column 3, first full par.. While Agrawal does not teach explicitly that or measure the functional property of a mucosal immune response generated as the result of an administration of a CpG motif containing oligo to the mucosal surface, such must necessarily follow as the result of the administration, particularly since both methods disclosed in Agrawal and the claims are identical. Note that a human subject who is identified as a cancer patient or one having an infectious agent is the same subject that is exposed to an antigen not encoded in a nucleic acid vector.

Claims 1, 11, 21, 23, and 24 are rejected under 35 USC 102(e) as being anticipated by Krieg (US Pat NO. 6,218,371).

With respect claimed embodiments, drawn specifically to a combined use of a CpG motif containing oligo and a cytokine in a subject exposed to an antigen such as subject at risk of having an allergic reaction, or asthmatic subjects, Krieg teaches that the CpG motif containing oligos are also effective for use in combination with an antigen against an allergen or in an asthmatic patient. See entire disclosure, column 8, lines 47-64, column 4, first full par., column 6, last full par., and column 12, first full par.

Claims 1, 3-7, 11-13, 15-23, 26-28, and 125-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hutcherson or Agrawal, each of which taken with Krieg (WO 96/02555) or Krieg (US Pat No. 6,239,116 B1).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by an administration to the mucosal surface of subject in need of an mucosal immune response *e.g.,* intranasal administration to a subject exposed to an antigen such as tumor antigen, viral particles, dust, pollen, antigenic molecules contained in the air or in contact with the subject, of an oligonucleotide (which can be complexed with any known colloidal dispersion system including lipid based system) having a length of 8 to 100 nucleotide residues and comprising CpG motif containing oligonucleotide having the generic formula: 5' X1X2CGX3X4 3' wherein C is unmethulated, and wherein X1, X2, X3 and X4 is any nucleotide residue. In this rejection, claimed embodiments drawn to a combined administration of an antigen and the above CpG motif containing oligo are applicable are applicable as set forth in the following paragraphs.

Hutcherson teaches a method of stimulating a local immune response in selected cells or tissues of an infectious subject or tumor bearing subject, the method comprising administering intranasally (see column 7, column 1, last first par.) to the subject a synthetic or ISIS oligo or an phosphoriioate oligonucleotide analog containing an unmethylated CpG motif, see the sequence listing as set forth in columns 15 and 16. Also see the claims. Ophthalmical, vaginal or rectal administration is also disclosed depending on a target tissue or cells targeted for an administration. While Hutcherson does not teach explicitly that functional property of a mucosal immune response has been generated as the result of an administration of an ISIS oligo to the mucosal surface, such must necessarily follow as the result of the administration, particularly since both methods disclosed in Hutcherson and the claims are identical. Phosphorothioate oligo analogs or phosphorothioate backbone modification is disclosed on column 8, lines 45-58. Pharmaceutical compositions comprising an ISIS oligo and a known vector carrier is disclosed on column 7, lines 52-55. Furthermore, Hutcherson teaches on column 8, lines 57-58, that liposomes and cationic lipids can significantly enhance the uptake of oligos.

Agrawal teaches a method of stimulating an immune response and/or cytokines production in an infectious animal or tumor bearing animals, the method comprising administering intranasally (see column 5, lines 40-56) to the subject a synthetic oligo containing an unmethylated CpG motif, wherein the oligo has the generic formula: 5' X1X2CGX3X4 3' wherein C is unmethulated, and wherein X1, X2, X3 and X4, see column 3, first full par.. While Agrawal does not teach explicitly that or measure the functional property of a mucosal immune response generated as the result of an administration of an

CpG motif containing oligo to the mucosal surface, such must necessarily follow as the result of the administration, particularly since both methods disclosed in Agrawal and the claims are identical.

Both Hutcherson and Agrawal do not teach explicitly an administration of an antigen, although Hutcherson clearly teaches that an ISIS oligo is administered in conjunction with a therapeutic agent such as an antiinfective or anticancer drug, see column 7, third par. Both also do not teach that the subject is one that is identified as one at risk of having an allergic reaction or that an asthmatic subject is embraced, that a colloidal dispersion system is used as a carrier of an CpG motif containing oligo, *e.g.,* lipsome or lipid based system.

However, at the time the invention was made, the concept of employing both a classical antigen and a CpG containing oligo for an induction of an immune response in a subject in need thereof, such as subjects at risk of having an allergic reaction, cancer, or asthma, is well-known in the prior art, as evidenced by the disclosure of both the '555 and the '116 reference. In fact, it is well-known in the prior art, as evidenced by the totality of the prior art of record, that Krieg holds numerous patents drawn to this subject matter. More specifically, and as an example, Krieg teaches the identical concept throughout the disclosure (pages 7, 10, 11, 13 and 14, for example). More specifically, on pages 21 and 22, any mode of administration of the oligo and/or antigen is disclosed. CpG motifs including 5' GTCpGTT and AACpGTT are also encompassed by the disclosure of Krieg. The same is disclosed on columns 6 and 7, column 10, column 13, third full par., column 45, particularly lines 36-46, column 46, second and third full pars. of the '116 patent.

It would have been obvious for one of ordinary skill in the art to employ an ISIS oligo of Hutcherson or a CpG motif containing oligos taught in either Agrawal or Krieg(s) in combination with a classical antigen for use in a method of inducing an immune response, wherein an intranasal administration route or any traditional route of administration as disclosed in the primary references is employed. One would have been motivated to administer a classical antigen concurrently, prior, or after an administration of an CpG motif containing oligo at the same site or a different site of a subject in need of an immune response such as allergy exposed subject, tumor containing subjects, subject at risk of having a cancer, or asthmatic patients because combination use of a therapeutic agent or vaccinated agent is well known in the prior art, as evidenced by the Hutcheson reference, and because Krieg(s) and claim and disclose in details this well-known concept. A reasonable person of ordinary skill in the art would have expected that the combination use of an antigen and a CpG containing oligo would enhance an immune response in a subject in need thereof, and thereby provide an additional therapeutically enhanced or partially protective response in the subject.

One of ordinary skill in the art would also have been motivated to employ liposomal or lipid based carriers known in the prior art as a carrier of the oligos taught by the combined cited references. One of ordinary skill in the art would have been motivated to employ lipid based carriers because even the Hutcherson reference teaches explicitly that liposomes and cationic lipids can significantly enhance the uptake of oligos, and because both Krieg(s) disclosed that liposomes or lipid based delivery complexes can be used as an oligo delivery complex. Along the same reasonings as set forth immediately above, one of ordinary skill in

the art would naturally follow up the initial dose of a CpG containing motif with an additional boost of an CpG containing oligo so as to further maintain or enhance an induction of the immune response in the treated or vaccinated subject.

Thus, the claimed invention, as a whole, was *prima facie* obvious.

Claims 1, 8, and 9 are rejected under 35 U.S.C. 103 as being unpatentable over are rejected under 35 U.S.C. 103(a) as being unpatentable over Hutcherson or Agrawal, each of which taken with Krieg (WO 96/02555) or Krieg (US Pat No. 6,239,116 B1), and further in view of Krieg *et al.* (Trends In Mircobiology, Vol. 6, No. 1, pp. 23-27, 1998).

The rejection of the base claim 1 is applied here as indicated above. To the extent that the references do not teach the use of an immune response induced-adjuvant including alum in the methods, Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines.

Thus, it would have been obvious for one of ordinary skill in the art to have employed alum in the immunization methods of the combined cited references, as indicated above. One of ordinary skill in the art would have been motivated to have employed alum as an adjuvant in the methods of the combined cited references because Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines. As such, one of ordinary skill in the art would readily recognize that such enhancement of a Th2 response as the result of the use of the adjuvant would further

generate at minimum a combined effects of various arms of immune response in the treated subject against a foreign antigenic molecule.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1, 11, 21, 23, 24, and 25 are rejected under 35 U.S.C. 103 as being unpatentable over Krieg (US Pat No. 6218371), Hutcherson or Agrawal, each of which taken with Krieg *et al.* (US Pat No. 6,218,371) and Craig (US 6,689,757)

The rejection of the base claim 1 is applied here as indicated above. To the extent that the references do not teach the use of a cytokine such as a B7 costimulary molecule in the methods, Krieg in the '371 patent teaches a cytokine as an adjuvant in combination with the CpG containing oligo of at least 8 nucleotides is disclosed on column 8, 25, 26 and 29, for example.

In addition, Craig specifically teaches on column 6:

> In a further embodiment of the present invention the DNA may encode additional factors which will have the effect of upregulating the immune response to the encoded antigen, or protein/peptide component of the delivery system. The additional factors may include cytokines for the general upregulation of specific components of the immune response e.g. interferon gamma, IL-2, IL-4, IL-10, IL-12, and GM-CSF; lymphokines; or co-stimulatory molecules such as B7-1, B7-2, ICAM-1 and ICAM-3. Alternatively, each factor may be included in a mixture of complex according to the invention in its polypeptide form, in that it may be co-administered with a nucleic acid and antigen according to the invention or it may be conjugated to the antigen or to a nucleic acid binding peptide so as to form part of the delivery complex.

One of ordinary skill in the art would have been motivated to employ a B7 costimulatory molecule in combination with an antigen/oligo composition as taught by the combined cited references. One of ordinary skill in the art would have been motivated to administer a cytokine such as a B7 costimulatory molecule because Krieg in the '371 patent in combination with Craig teach that such combination use would effectively ensure not only an additional enhancement of an immune response but also a synergistic effect of the immune response generated by both in combating infectious or antigenic agents.

Thus, the claimed invention was *prima facie* obvious.

Claims 1, 3-9, 12-13, 15-20, 22, 26-28, and 125-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Hutcherson and Agrawal.

Briles et al. disclose an immunogenic composition and a method for eliciting an immunological response against pneumococcal surface protein A (PSPA) in a host susceptible to *Streptococcus pneumoniae* by intranasally administering to the host an effective amount of PSPA in the form of a killed whole pneumococci, a lysate of pneumococci or an isolated PSPA or an immunogenic fragment thereof in the presence of an adjuvant, with cholera toxin B as a preferred adjuvant, to protect a host against pneumoccocal colonization and/or systemic infection (see summary of invention, col. 1-7). Briles et al. also teach that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or

attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. Briles further disclose that the immunogenic composition can be prepared as inhalables, sprays and that pump spray or nasal spray or squeeze dispensers (a device) for dispensing a metered dose or a dose with a particular particle or droplet size are commercial available for mucosal administration (col. 3, lines 32-52). Briles et al. further teach that useful surfactants for the immunogenic composition include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate and others to enhance absorption (col. 6, lines 14-21). Briles et al. further teach that specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts, as well as predominantly IgA antibody secreting cells in the intestinal lamina propria and salivary glands. Strong circulatory immune responses are also induced with IgG and IgA antibodies in the serum, and IgG and IgA antibody-secreting cells in the spleen (col. 8, lines 14-34, and examples). Briles et al. do not teach the use of any immunostimulatory oligonucleotide, including a core nucleotide sequence having the formula: 5'-Purine-Purine-[C]-[G]-Pyrimidine-Pyrimidine-3' or one having the core nucleotide sequence of the elected species as an additional immunostimulatory molecule in a composition or a method for inducing mucosal immunity to an antigen in a mammalian host via intranasal administration.

However, at the effective filing date of the present application, Hutcherson teaches a method of stimulating a local immune response in selected cells or tissues of an infectious

subject or tumor bearing subject, the method comprising administering intranasally (see column 7, column 1, last first par.) to the subject a synthetic or ISIS oligo or an phosphoriioate oligonucleotide analog containing an unmethylated CpG motif, see the sequence listing as set forth in columns 15 and 16. Also see the claims. While Hutcherson does not teach explicitly that functional property of a mucosal immune response has been generated as the result of an administration of an ISIS oligo to the mucosal surface, such must necessarily follow as the result of the administration, particularly since both administering steps as disclosed in Hutcherson and the claims are identical. Phosphorothioate oligo analogs or phosphorothioate backbone modification is disclosed on column 8, lines 45-58. Pharmaceutical compositions comprising an ISIS oligo and a known vector carrier is disclosed on column 7, lines 52-55. Furthermore, Hutcherson teaches on column 8, lines 57-58, that liposomes and cationic lipids can significantly enhance the uptake of oligos.

Agrawal teaches a method of stimulating an immune response and/or cytokines production in a subject so as provide protection against infection by pathogenic agents (see column 3, lines 50-54), the method comprising administering intranasally (see column 5, lines 40-56) to the subject a synthetic oligo containing an unmethylated CpG motif, wherein the oligo has the generic formula: 5' X1X2CGX3X4 3' wherein C is unmethulated, and wherein X1, X2, X3 and X4, see column 3, first full par.. While Agrawal does not teach explicitly that or measure the functional property of a mucosal immune response generated as the result of an administration of an CpG motif containing oligo to the mucosal surface,

such must necessarily follow as the result of the administration, particularly since both intranasal administering steps as disclosed in Agrawal and the claims are identical.

Accordingly, it would have been obvious for an ordinary skilled artisan, to modify the immunogenic composition (including a kit that has pump spray or nasal spray or squeeze dispensers for dispensing a metered dose or dose with a particular size of the immunogenic composition) and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing an immunostimulatory oligonucleotide having the CpG motif as taught by either Hutcherson or Agrawal in either a free form or in a non-covalently linkage with PSPA antigens as an adjuvant (It is noted that it is well known in the art of vaccine that antigen is normally conjugated to an adjuvant to enhance the host immune response as also evidenced by the teachings of Briles *et al.*) . One of ordinary skilled artisan would have been motivated to carry out the above modification simply because Hutcherson teaches that an immunomodultory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or therapeutic agent in a pharmaceutically acceptable carrier, as an immunostimulatory molecule so as to boost a local immune response at selected cells or tissue, thereby effecting a better combined response from the vaccine and immunostimulatory molecules, and because Agrawal teaches that an enhanced production of cytokines as the result of using an CpG motif containing oligo would provide a better protection in a subject against an infection by a pathogenic agent.

One of ordinary skill in the art would also have been motivated to employ a cationic lipid base carrier or a liposome as a carrier of the oligo based immunostimulatory molecule.

One of ordinary skill in the art would have been motivated to employ a cationic lipid based carrier or a liposome as a carrier of an CpG motif containing oligo because Hutcherson teaches that liposomes and cationic lipids can significantly enhance the uptake of oligos in target cells. Also, in order to further effect a long lasting or continuous effect of a mucosal immune response against a pathogen, one of ordinary skill in the art would naturally follow up the initial dose of an antigen and/or CpG containing motif with an additional boost of the antigen and/or CpG containing oligo so as to further maintain or enhance an induction of the immune response in the treated or vaccinated subject.

Thus, the claimed invention as a whole, was *prima facie* obvious.

Claims 1, 3-9, 12-13, 15-20, 22, 26-28, and 125-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Hutcherson and Agrawal, and further in view of Krieg (WO 96/02555).

To the extent that the claims embrace the elected species of oligos such as AACpGTT and GTCpGTT, the rejection of all of the claims as being unpatentable over Briles taken with Hutcherson and Agrawal is applied here as set forth above. The use of numerous immunostimulatory CpG motif containing oligos in combination with an antigen, as evidenced by the teaching of Krieg. More specifically, and as an example, Krieg teaches the identical concept throughout the disclosure (pages 7, 10, 11, 13 and 14, for example). More specifically, on pages 21 and 22, any mode of administration of

the oligo and/or antigen is disclosed. CpG motifs including 5' GTCpGTT and AACpGTT are also encompassed by the disclosure of Krieg.

It would have been obvious for one of ordinary skill in the prior art to employ any of the known CpG including those containing 5' GTCpGTT and AACpGTT in the method of Briles taken with Hutcherson and Agrawal. One would have been motivated to do so as a minor modification or equivalent design, since Krieg teaches that X1X2CpGTT, wherein X1 and X2 can be any nucleotide, which includes the GTCpGTT motif and AACpGTT, is an effective immunostimulatory molecule for use in combination with any known classical antigen as a vaccine or immunogenic composition.

Thus, the claimed invention was *prima facie* obvious.

Claims 1, 24, and 25 are rejected under 35 U.S.C. 103 as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Hutcherson and Agrawal, and further in view of Craig (US 6,689,757)

The rejection of the base claim 1 is applied here as indicated above. To the extent that the references do not teach the use of a cytokine such as a B7 costimulary molecule in the methods, Craig in the '757 patent teaches that cytokines are effective for use in a combination vaccine or complex (entire disclosure). Craig specifically teaches on column 6:

> In a further embodiment of the present invention the DNA may encode additional factors which will have the effect of upregulating the immune response to the encoded antigen, or protein/peptide component of the delivery system. The additional factors may include cytokines for the general upregulation of specific components of the immune response e.g. interferon gamma, IL-2, IL-4, IL-10, IL-12, and GM-CSF; lymphokines; or co-stimulatory molecules such as B7-1, B7-2, ICAM-1 and ICAM-3. Alternatively, each factor may be included in a mixture of complex according to the invention in its polypeptide form, in that it may be co-administered with a nucleic acid and antigen according to the invention or it may be conjugated to the antigen or to a nucleic acid binding peptide so as to form part of the delivery complex.

One of ordinary skill in the art would have been motivated to employ a B7 costimulatory molecule in combination with an antigen/oligo composition as taught by the combined cited references. One of ordinary skill in the art would have been motivated to administer a cytokine such as a B7 costimulatory molecule because K Craig teaches that such combination use would effectively ensure not only an additional enhancement of an immune response but also a costimulatory effect of immune responses generated by both in combating infectious or antigenic agents.

Thus, the claimed invention was *prima facie* obvious.

Applicant's response (pages 10-13) has been considered but is moot in view of new grounds of rejection. To the extent that applicant discusses the Davis Declaration and asserts that the Declaration is sufficient to antedate the effective filing date of the '371 patent, the discussion and/or assertion are not found persuasive because of the reasons as

set forth previously. Note that the Declaration does not provide any evidence with respect to the combination use of a cytokine and a CpG containing motif in combating a subject at risk of having an allergic reaction or in an asthmatic patient, which combination use is disclosed and claimed in the '371 patent and relied mainly by the examiner in the above stated rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632